

Citation:

Ginsberg GL, Toal BF. Quantitative approach for incorporating methylmercury risks and omega-3 fatty acid benefits in developing species-specific fish consumption advice. *Environ Health Perspect.* 2009 Feb; 117: 267-275.

PubMed ID: [19270798](#)

Study Design:

Risk/benefit analysis

Class:

M - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To develop a method to quantitatively analyze the net risk/benefit of individual fish species for adult cardiovascular and in-utero neurodevelopmental end-points based on the methylmercury (MeHg) and omega-3 fatty acid (omega-3 FA) content of those fish.

Inclusion Criteria:

Not specified for selected studies used in this research.

Exclusion Criteria:

Not specified for selected studies used in this research.

Description of Study Protocol:**Recruitment**

Selected studies from literature that supported an integrated risk/benefit analysis for adult cardiovascular and in utero neurodevelopmental end points on a fish species-specific basis.

Design

- Authors selected studies from the literature to support an integrated risk/benefit analysis for adult cardiovascular and in utero neurodevelopmental end points on a species-specific basis; these studies examined risk/benefit between specific fish species and:
 - Cardiovascular disease in adults: CHD mortality [fatal myocardial infarction (MI) and sudden death] or first MI; for these studies, examined:
 - Omega-3 FA benefit: Reported slope for change in relative risk per 100mg per

- day intake of EPA+DHA unadjusted for countervailing effect of MeHg
- Dose response for MeHg effects on MI based on the relationship between toenail mercury and MI odds ratios
- Neurodevelopment in six-month-old infants: Visual recognition memory, VRM (a test that evaluates infant's ability to encode a stimulus into memory and recognize a new stimulus as novel and preferential to the old stimulus and is predictive of IQ at later developmental stages); for these studies, examined:
 - Common end point for both omega-3 FA and MeHg because these agents have opposite effects in mother-infant pairs
 - Slope for hair mercury effect on VRM score
- List of fish chosen for analysis included those commonly available in Connecticut markets and for which MeHg and omega-3 FA data were available
- MeHg fish concentration (micrograms per gram) was converted to hair MeHg concentration; toenail mercury biomonitoring data was converted to hair mercury.

Dietary Intake/Dietary Assessment Methodology

Not applicable.

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

- Dose-response functions were run to estimate the effect of at least one fish meal per week on the outcome measure using these risk/benefit equations:
 - **Net risk/benefit for adult CHD** = $[(\text{omega-3 FA mg per meal}) \times (\text{number of meals per week}) \times (\text{one week/seven days}) \times (14.6\% \text{ lower risk}/100\text{mg omega-3 FA})] - \{[(\text{hair Hg change/fish meal}) \times (\text{number of meals per week})] - (0.5 \text{ ppm hair Hg})\} \times (23\% \text{ higher risk}/1 \text{ ppm hair Hg})$
 - **Net risk/benefit for infant VRM** = $[(\text{omega-3 FA mg/meal}) \times (\text{number of meals per week}) \times (\text{one week/seven days}) \times (\text{two VRM points}/100\text{mg omega-3 FA})] - [(\text{hair Hg change per fish meal}) \times (\text{number of meals per week}) \times (7.5 \text{ VRM points per } 1 \text{ ppm hair Hg})]$
- Species that yield a positive result from equations have a net benefit, whereas a result less than one signifies an increased risk
- Equations contain exposure components based on the number of fish meals eaten per week and the MeHg and omega-3 FA species-specific content of the fish
- Model assumptions:
 - Meal size of six-ounce (170g) of fish
 - 95% absorption of MeHg in gastrointestinal tract
 - MeHg elimination rate equal to 1.4% of body burden per day
 - Long-term consumption of one meal per week for several months, enough time to reach steady-state blood and hair concentrations of MeHg
 - Omega-3 FA benefit requires consistent exposure over time, and that no other fish were consumed besides one meal per week of indicated species.

Data Collection Summary:

Timing of Measurements

- For adult CVD endpoints, no information provided on timing of measurements of end-points
- For neurodevelopmental endpoint: Measured VRM in 135 mother-infant pairs at six months after birth.

Dependent Variables

- Adult CVD end-points:
 - Adult fatal MI or sudden death
 - Adult first MI.
- Neurodevelopmental end-point:
 - Visual recognition memory score among six-month old infants.

Independent Variables

- For adults CHD risk: mg omega-3 fatty acid content of meal; number of fish meals per week; hair Hg content
- For infant VRM: mg omega-3 fatty acid content of meal; number of fish meals per week
- Intake of EPA+DHA as reflected in omega-3 fatty acid content of 16 species of fish
- MeHg intake as reflected in hair and toenail MeHg content resulting from consumption of 16 species of fish.

Control Variables

Not explicitly stated.

Description of Actual Data Sample:

- *Initial N:*
 - Five studies chosen to perform integrated risk/benefit analysis of the effects of omega-3 fatty acid and MeHg intake on adult CVD outcomes and infant neurodevelopment
 - For adult CVD risk/benefit analysis: Combined data across 20 studies for EPA-DHA intake vs. CHD mortality from one of the five studies
 - For neurodevelopmental risk/benefit analysis: Measured VRM in 135 mother-infant pairs
- *Attrition (final N):*
 - Five studies chosen to perform dose-response relationship and integrated risk/benefit analysis of the effects of omega-3 fatty acid and MeHg intake on adult CVD outcomes and infant neurodevelopment
 - For adult CVD risk/benefit analysis: Combined data across 20 studies for EPA-DHA intake vs. CHD mortality from one of the five studies
 - For neurodevelopmental risk/benefit analysis: Measured VRM in 135 mother-infant pairs
- *Age:* Age of adults in chosen studies and mother-infant pairs in chosen study not provided
- *Ethnicity:* Ethnicity of adults in chosen studies and mother-infant pairs in chosen study not provided
- *Other relevant demographics:* Other demographics of adults in chosen studies and

mother-infant pairs in chosen study not provided

- *Anthropometrics*: Not provided for any of studies used
- *Location*: Not provided for any of studies used.

Summary of Results:

Key Findings

- Estimated omega-3 FA benefits outweigh MeHg risks for farmed salmon, herring, and trout
- Estimated omega-3 FA benefits do not outweigh MeHg risk for swordfish and shark
- A small net benefit is associated with consumption of flounder and canned light tuna
- A small net risk is associated with consumption of canned white tuna and halibut
- Effect of meal frequency:
 - Marginal benefit of tilapia, pollack, flounder and shrimp may increase with greater meal frequency
 - Negative impacts of swordfish and shark and beneficial effects of trout, farmed salmon, and herring would be magnified as consumption increases; presence of other contaminants should be considered when recommending frequent consumption
- Net benefit or risk is contingent upon ratio of omega-3 FA to MeHg in the fish, which does not change when analyzing different end-points
- The risk/benefit ratio is more in the benefit direction for CHD mortality compared with VRM score; saturation of benefit is speculative for cardiovascular risk and not evident for neurodevelopmental risk
- Substantial risk for ingestion of swordfish or shark; approximately 50% worsening of relative risk for MI
- Separate advice for neurodevelopmental risk group vs. the cardiovascular risk group, because of greater net benefit from fish consumption for the cardiovascular risk group
- Four consumption categories can be used to illustrate the potential utility of the model, and consumption rates used as a point of comparison with those recommended by FDA, EPA and various medical and public health authorities
- The risk/benefit analysis provides:
 - Risk/benefit support for separate two meal and one meal per week categories
 - Additional fish to include in once weekly consumption category
 - Useful framework for analyzing species-specific risks and benefits for deriving fish advisories and highlighting beneficial fish and discouraging consumption of riskier species for a wide variety of commercially available and locally caught fish, assuming MeHg and omega-3 FA data are available
 - Omega-3 FA dose-response functions which capture overall benefit of fish consumption with the exception of that from fish oil supplements
- Individuals can consume safely one six-ounce meal per day for seven out of the 16 seafood species modeled taking into account infant neurodevelopment, and for nine of these species when modeling cardiovascular health.

Table: Dose-response Relationships for Key MeHg and Omega-3 FA End-points

End-Point	Agent	Dose Response	Comments
-----------	-------	---------------	----------

Adult CHD Mortality	Omega-3 fatty acids	14.6% decreased RR per 100mg per day	Combined data across 20 studies for EPA+DHA intake versus CHD mortality; possible saturation of benefit at >250mg per day
Adult MI risk	Methylmercury	23% increased RR per 1ppm hair Hg	Slope adjusted for DHA content of lipid as index of fish oil intake; risk not apparent <0.51ppm hair HG; toenail HG measured, but converted to ppm in hair
Infant VRM score	Omega-3 fatty acids	2.0-point increase per 100mg per day	VRM measured at six months in 135 mother-infant pairs; fish oil intake estimated from dietary survey
Infant VRM score	Methylmercury	7.5-point decrease per 1ppm hair Hg	VRM measured at six months in 135 mother-infant pairs; direct measurement of maternal hair Hg

Author Conclusion:

- If the studied population ingests more beneficial fish, this can create the appearance of a generalizable positive association in the absence of information on the actual species consumed. These analysis point out the importance of looking at individual species, because the risk/benefit ratio may vary considerably across species
- A species-by-species approach to consumption advisories is particularly meaningful given that many people have favorite fish they eat most often. The goal of the species-specific approach is to encourage people to eat from a variety of fish, focusing on the most beneficial species
- Analysis are supportive of FDA and EPA advisories showing sword-fish and shark should not be eaten by women of childbearing age, and provide list of species potentially safe to consume more frequently than suggested by federal advisories, on the basis of neurodevelopmental and cardiovascular risks
- Research provides risk/benefit analysis framework that can be used to develop categories of consumption advice with the caveat that unlimited may need to be tempered for certain fish (e.g., farm-raised salmon) because of other contaminants and end points (e.g., cancer risk)
- Uncertainties exist in the underlying dose-response relationships, pointing in particular to the need for more research on the adverse effects of MeHg on cardiovascular end-points
- Analysis points to key research areas for improving risk/benefit analysis for fish consumption, and the demonstrated approach may serve as a model for analyzing fish species, contaminants and end-points not included in the present analysis.

Reviewer Comments:

- *Fish chosen for analysis were from Connecticut markets only*
- *Limited number of studies examined to test model.*

Limitations per authors:

- *Assumptions made that the omega-3 fatty acid benefit requires consistent exposure over time*

and that no other fish were consumed other than the one meal per week of the indicated species

- *Analysis is simplistic in only assessing two factors (i.e., only omega-3 fatty acids and MeHg) regarding fish ingestion that may influence the end-points of interest, the lack of examination of other nutrients and contaminants in fish and other endpoints of concern creates uncertainty regarding the overall health implications of fish consumption*
- *The assignment of consumption advice for individual species is tentative given limitations in the analysis, such as:*
 - *Dose-response relationships for the risks and benefits of these components are supported by available data, but do contain uncertainties (e.g., other nutrients besides omega-3 fatty acids may have contributed to observed benefits)*
 - *Authors made no attempt to separate out benefits from other nutrients in fish*
- *Regarding the omega-3 FA benefit:*
 - *Reported slope for change in relative risk per 100mg per day intake of EPA+DHA unadjusted for countervailing effect of MeHg may underestimate the true relationship or suggest a plateau in benefit that is an indication of MeHg toxicity*
 - *May saturate above a certain daily dose of about 250mg per day; saturation may be artificial due to increasing effects of MeHg at higher fish ingestion rates and evidence of no saturation of benefits in some studies, this analysis did not include a saturation function for the omega-3 FA benefit*
- *Dose response for MeHg effects on MI was based on the relationship between toenail mercury and MI odds ratios, which often overestimates cardiovascular benefit in terms of improved relative risk*
- *More extensive data for both omega-3 FA and MeHg content of fish (numbers and varieties of fish sampled, seasonal and source variation) are needed to improve confidence and understand variability in this key input data*
- *In the VRM study, the group that showed the MeHg effect was small (high hair mercury, low fish intake, N=12)*
- *These analysis were limited because each fish species was assessed in isolation from consumption of any other fish*
- *These analysis did not include variability in fish concentrations in omega-3 FA and MeHg, variability in the toxicokinetics of MeHg, and variability in response functions for omega-3 FA and MeHg*
- *There are numerous uncertainties regarding additional contaminants, nutrients, end-points, underlying dose-response functions, and comparison with other protein sources; these factors would require a more data intensive and complex analysis.*

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions

1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions

1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?	No
3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	???
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issues considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes